CORRESPONDENCE

Is TRIM11 Immunohistochemical Positivity Specific for the Diagnosis of CRTC1::TRIM11 Cutaneous Tumours?

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To the Editor,

We read with great interest the article by Koga et al. (1). This represents the first study detailing dermatoscopic features of this tumour and reporting its occurrence on the sole, significantly enriching the clinical understanding of CRTC1::TRIM11 cutaneous tumours (CTCT). However, we have concerns regarding the pathological findings and diagnostic criteria presented.

In terms of histopathology, the HE staining of the tumour shows irregular elongation of the overlying epidermis with keratosis, nodular lesions in the deep dermis with fibrosis, and aggregated tumour cells that are oval to spindle-shaped with mild nuclear atypia. This differs from the morphological characteristics of CTCT reported in previous literature (2–4). The lack of in-depth discussion and analysis of this discrepancy may affect readers' comprehensive understanding of the pathological features of this tumour.

Regarding the diagnostic criteria, the study detected positive SOX10 and TRIM11 through immunohistochemistry, and excluded EWSR1 fusion by break-apart fluorescence *in situ* hybridization (FISH). Based on our research experience, TRIM11 positivity cannot be regarded as a reliable basis for diagnosing CTCT cutaneous tumours. We encountered a case where TRIM11 immunohistochemistry showed diffuse positivity after HE staining, FISH verified the presence of TRIM11 fusion, and transcriptome sequencing further confirmed the CTCT (**Fig. 1**A, B). However, in another patient with similar clinical and pathological manifestations, although TRIM11 immunohistochemistry was positive, FISH detection did not identify TRIM11 fusion, and transcriptome sequencing also failed to detect the

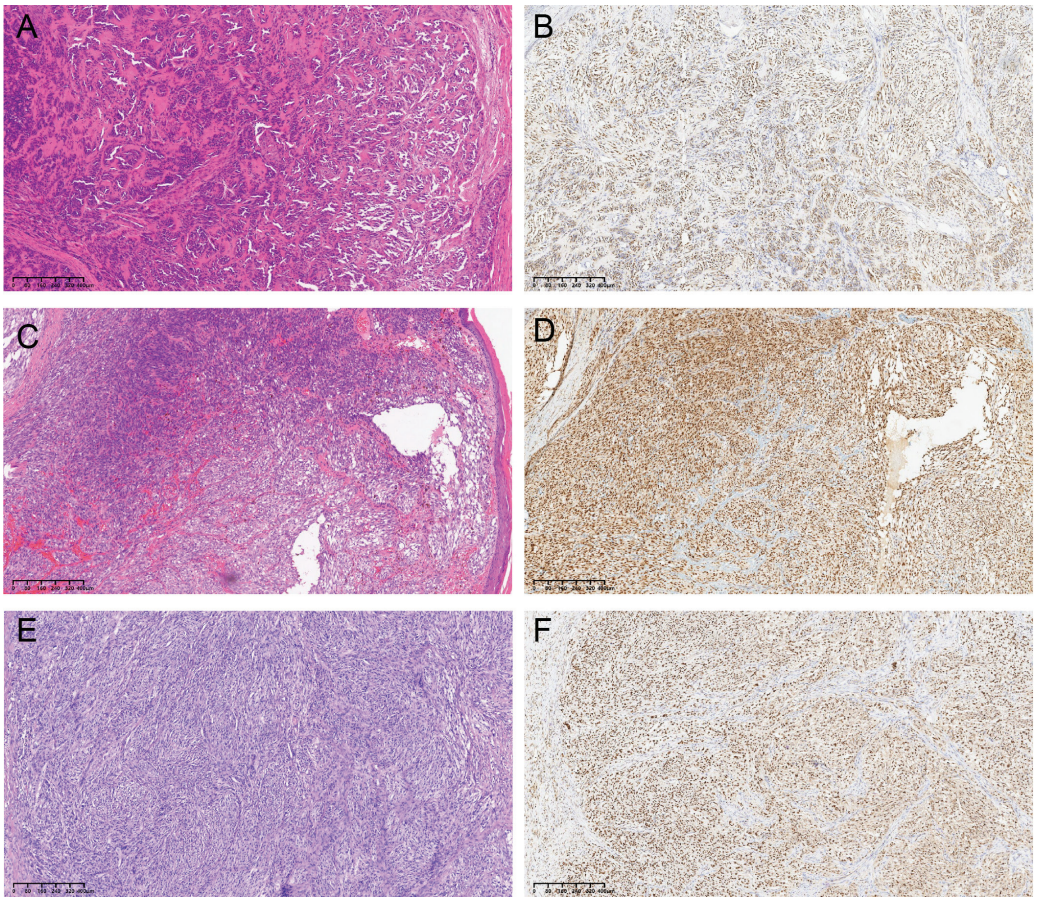

Fig. 1. Histological features and TRIM11 immunohistochemistry results of 3 patients. (A) HE staining and (B) TRIM11 IHC of a CTCT patient. (C) HE staining and (D) TRIM11 IHC of a melanoma patient with negative CRTC1::TRIM11 fusion. (E) HE staining and (F) TRIM11 IHC of a clear cell sarcoma patient, with EWSR1::ATF1 fusion revealed by RNA-seq. HE: haematoxylin–eosin; IHC: immunohistochemistry; CTCT: CRTC1::TRIM11 cutaneous tumour.

CRTC1::TRIM11 or EWSR1 fusion genes. This clearly indicates that TRIM11 positivity is not specific (Fig. 1C, D). Additionally, we performed TRIM11 immunohistochemistry on different types of melanomas and clear cell sarcomas, which are easily confused with CTCT tumours. The results showed that all samples were diffusely positive, further confirming the non-specificity of TRIM11 immunohistochemistry in diagnosis (Fig. 1E, F).

Based on these findings, we concur that HE morphology and TRIM11 IHC positivity can serve as important clues prompting consideration of a CTCT diagnosis. However, for definitive diagnosis, FISH detection confirming a TRIM11 rearrangement is more specific, and transcriptome sequencing confirming the CRTC1::TRIM11 fusion gene should be considered the diagnostic gold standard.

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Reply to: Is TRIM11 Immunohistochemical Positivity Specific for the Diagnosis of CRTC1::TRIM11 Cutaneous Tumours?

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We partially agree with the commentary by Chen et al. The diagnosis of CTCT should be comprehensive and must not rely solely on a single immunohistopathological stain. Meanwhile, we believe that the results of TRIM11 immunohistochemical staining can serve as a reference, although the significance has not yet been fully established.

In our case, we believed that clear cell sarcoma and melanoma could initially be excluded based on the morphology in haematoxylin and eosin (H&E) stained images. Additionally, we performed EWSR1 break-apart fluorescence *in situ* hybridization (FISH) and performed immunohistochemical stains, such as PRAME, to confirm the negative results. Eventually, we established the diagnosis based on all these findings, including TRIM11 immunostaining.

According to the World Health Organization (WHO) diagnostic criteria, differentiating clear cell sarcoma is essential for diagnosing CTCT, although the confirmation of the fusion gene through genetic testing is not stated as necessary.

We would like to emphasize that the most significant diagnostic findings are obtained from H&E stained images.